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Penetration of cefuroxime into the cerebrospinal fluid of patients with traumatic brain injury

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Cefuroxime levels were measured in cerebrospinal fluid (CSF) and serum of four patients with traumatic brain injury following the implantation of intraventricular catheters. The levels ranged from 0.15 to 2.03 μg/mL in CSF and from 1.8 to 66.9 μg/mL in serum. No ventriculostomy related infections were detected.

Introduction

Intracranial pressure (ICP) monitoring is fundamental in the treatment of patients with severe traumatic brain injury (TBI). Intraventricular catheters (IVC) allow continuous ICP monitoring as well as drainage of ventricular cerebrospinal fluid (CSF) in order to reduce elevated ICP. However, the risk of ventriculostomy related infections (VRI) exists (Rosner & Becker, 1976; Mayhall *et al.*, 1984; Clark *et al.*, 1989). In order to prevent VRI, an absolute aseptic surgical technique and sterile management is necessary while the catheter is in place. Detailed information on penetration of antibiotics into CSF of patients with TBI is lacking so the advantage of prophylaxis remains controversial (Mayhall *et al.*, 1984; Clark *et al.*, 1989). However, cefuroxime is routinely used in our clinic as a prophylactic antibiotic in patients with TBI during the time of ventricular ICP monitoring and may be of benefit. Cefuroxime levels were monitored in CSF and serum of patients with severe TBI who underwent ventriculostomy. Relevant antibiotic concentrations were detected in CSF independently from the integrity of the blood brain barrier.

Materials and methods

Patients

In 1994 a total of 31 patients with severe TBI received IVC at the Division of Trauma Surgery, University of Zürich, Switzerland. All of them had a Glasgow Coma Score (GCS) $\leqslant 8$ on arrival (Teasdale & Jennett, 1976) and showed varying abnormalities in the computed tomography (CT). Table I shows the clinical details of four patients

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included in this study. After surgical treatment the patients were transferred to the intensive care unit (ICU). The therapy followed a standardized protocol (Stocker *et al.*, 1995). VRI was diagnosed according to Mayhall (Mayhall *et al.*, 1984) and pneumonia was diagnosed according to the protocol (Stocker *et al.*, 1995). The study was approved by the University Hospital Medical Ethics Board, Zürich.

Intraventricular catheter insertion

IVC (Becker External Drainage, Pudenz-Schulte Medical Corporation, Goleta, CA, USA) were used in brain injured patients for monitoring as well as for therapeutic release of CSF when ICP exceeded 15 mmHg. The IVC were inserted under aseptic conditions in the operating room.

Cefuroxime treatment

Cefuroxime (Zinacef®, Glaxo AG, Schoenbuehl, Switzerland) was given in all patients prior to IVC implantation in doses of 1.5 g intravenously and continued at the same dosage every 8 h for 10–25 days (Table I). Cefuroxime was administered as recommended by the manufacturer.

Specimen collection and microbiology

The serum and CSF samples were drawn on day 2, 4 and 6 of the treatment period at approximately 1.5 and 6 h (99 ± 13 min and 355 ± 8 min respectively, mean ± S.E.M.) after the first dose of cefuroxime. The specimens were centrifuged at 170 **g** at 4°C for 10 min, divided into aliquots and frozen at −70°C until analysis.

On a routine basis CSF samples were drawn every three to four days and screened for bacterial infections. The IVC tips were tested after removal for bacterial colonisation at the Institute for Medical Microbiology, University of Zürich.

Albumin analysis and blood brain barrier function

Albumin levels were measured in CSF and serum by automatized laser photometry (BNA Automat, Behring Werke, Marburg, Germany). The CSF/serum albumin ratio (Q_A) was utilized as a parameter for blood brain barrier (BBB) integrity (Reiber & Felgenhauer, 1987).

High performance liquid chromatography (HPLC) analysis

Cefuroxime levels were determined by a reversed phase HPLC system (Waters-Millipore Corp., Milford, MA, USA) using 40% methanol in 5 mM tetrabutylammoniumphosphate as mobile phase and photodiode array detection. The variability of the assay was <3%, linearity was tested at 1.5–150 μg/mL, detection limits for serum and CSF samples were 0.2 and 0.1 μg/mL respectively.

Results and discussion

At our institution cefuroxime is used as a standard prophylactic antibiotic not only in patients with severe TBI. In this study all patients received an IVC for measurement and treatment of elevated ICP. Additionally the IVC offered the possibility of a continuous monitoring of cefuroxime levels in the cerebral compartment. Table I summarizes the clinical data. The IVC was in place for 20 to 26 days. Patient selection was based on the single antibiotic prophylaxis with cefuroxime which was given from the day of insertion and continued for at least 10 days (Table I). Our results clearly show that cefuroxime enters the CSF of patients with TBI. Cefuroxime concentrations in CSF ranged from 0.35 to 1.76 μg/mL at approximately 1.5 h after the first daily application of cefuroxime (day 2, 4 and 6), whereas after about 6 h the levels ranged from 0.15 to 2.03 μg/mL (Figure). The corresponding levels of cefuroxime in serum ranged between 2.0 and 61.7 μg/mL after 1.5 h and between 1.8 and 66.9 μg/mL after 6 h. As indicated in the figure, two samples (patient 2 at day 6 and patient 4 at day 2) were collected later (after the second daily dose) and therefore these concentrations were higher. The cefuroxime levels in the serum of our patients were highly variable. The use of IVC in the treatment of brain injured patients is nowadays well established (Stocker *et al.*, 1995), despite the risk of infections (Mayhall *et al.*, 1984; Clark *et al.*, 1989). The device must be implanted under aseptic conditions and the removal of CSF has to be performed under sterile conditions.

The use of prophylactic antibiotics in patients with IVC is controversal (Mayhall *et al.*, 1984; Clark *et al.*, 1989), chiefly due to the fact that the penetration of antibiotics in the CSF of patients with severe TBI has not been studied, whereas numerous pharmacokinetic studies have been performed in patients with meningitis (Ristuccia & Le Frock, 1992).

Cefuroxime is a second generation cephalosporin with a broad antimicrobial spectrum (Ristuccia & Le Frock, 1992) and is active against frequently encountered bacteria, which can cause meningitis following neurosurgical procedures (Mayhall *et al.*, 1984). Cefuroxime reaches therapeutic concentrations in many body compartments (Daikos *et al.*, 1977), has a very low toxicity, and is excreted unmetabolized by the urinary tract (Ristuccia & Le Frock, 1992). In meningitis cefuroxime has superior penetration into the CSF compared to other cephalosporins (Daikos *et al.*, 1977; Ristuccia & Le Frock, 1992). In children with bacterial meningitis mean cefuroxime concentrations in the CSF were 6.4 and 3.6 μg/mL 2 h following iv doses of 50 mg/kg of cefuroxime on days 2 and 14 of treatment. Without meningeal inflammation mean cefuroxime concentration in CSF was 1.34 μg/mL (Sirinavin *et al.*, 1984). This finding is comparable with our results. The minimal inhibitory concentration for sensitive staphylococci and streptococci ranges from 0.1 to 1.4 μg/mL. Therefore, cefuroxime concentrations in CSF of our patients are likely sufficient to inhibit most of the bacteria found in VRI (Mayhall *et al.*, 1984).

No patient in this study had a VRI, which was confirmed by microbiological analysis of the CSF samples every 3 to 4 days during the period the IVC was in place. Furthermore, the IVC-tips of all patients were analyzed after removal for bacterial colonisation, but no bacterial infection was detected.

Systemic infections occurred during their treatment period in the ICU. The onset of these infections was more than a week (7–14 days) following TBI. Three out of four patients had pneumonia (Table II). The cefuroxime monotherapy was supplemented

Table I. Clinical details of the four patients studied

Patient	Sex/age (years)	Other injuries	Duration IVC[a] (days)	Days in ICU[b]	GOS[c]	VRI[d]	Antibiotic prophylaxis	Duration (days)
1	M/41	fractures of humerus, tibia, calcaneus and patella	20	31	5	no	cefuroxime	21
2	F/23	fracture of radius	24	35	5	no	cefuroxime	25
3	M/16	facial fractures	26	28	4	no	cefuroxime	10
4	F/18	fracture of radius	20	31	5	no	cefuroxime	16

[a]Duration of intraventricular catheter in place.
[b]Intensive care unit.
[c]Glasgow Outcome Score at 6 months after trauma (Jennett *et al.*, 1976)
[d]Ventriculostomy related infections.

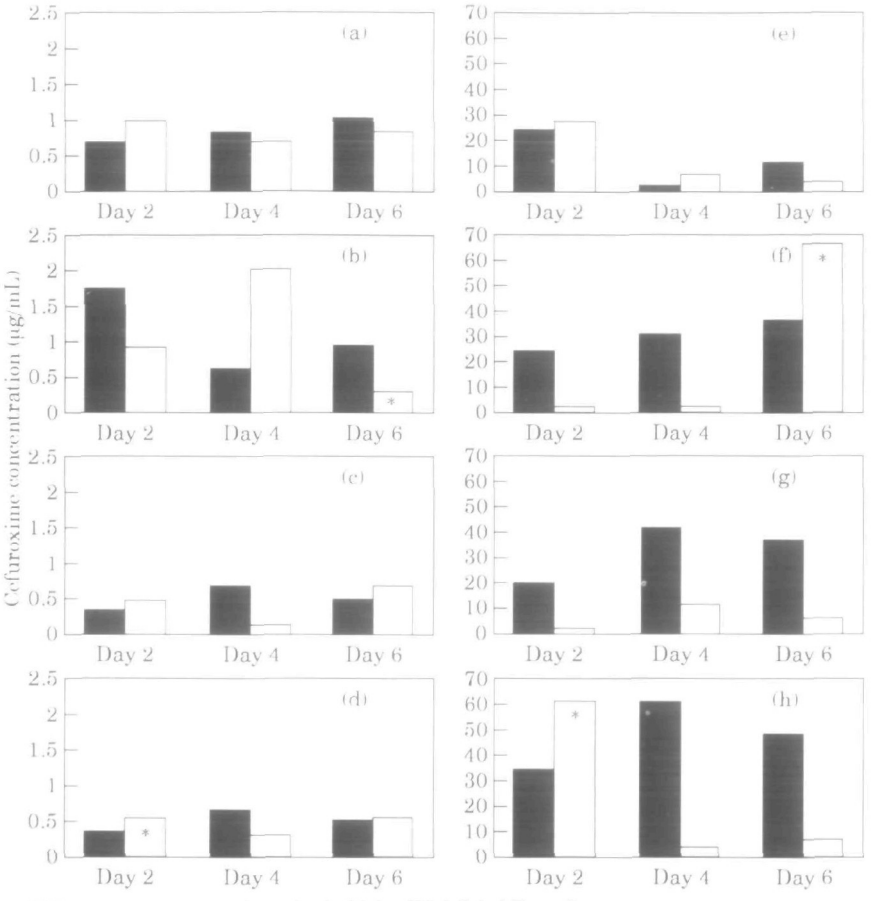

Figure. Cefuroxime concentrations (μg/mL) in CSF ((a)–(d)) and serum ((e)–(h)) of four brain injured patients. Black columns show values after 1.5 h (99 ± 13 min) and white columns after 6 h (355 ± 8 min). As indicated by asterisk (*) two samples (patient 2 at day 6 and patient 4 at day 2) were drawn after the second daily administration of cefuroxime The CSF and serum levels reflect concentrations 45 min (patient 2) and immediately (patient 4) after the second daily infusion of cefuroxime.

with different antibiotics according to microbiological evaluation of the bronchoalveolar lavage and may have delayed the occurrence of VRI. However, previously the onset of VRI has been reported predominantly within 5 days after insertion of the IVC (Mayhall *et al.*, 1984; Clark *et al.*, 1989).

After a 6 month period the patients were examined again and none showed clinical signs of late onset intracerebral infection. They had recovered to a varied extent and had a GOS between 4 and 5 (Jennet *et al.*, 1976).

In order to determine the influence of BBB function on the availability of cefuroxime we analyzed the CSF/serum albumin ration (Q_A). With the exception of patient 2, who showed a moderate dysfunction of the BBB during the first 48 h, the Q_A of all patients were below 0.007 indicating normal BBB function. Therefore, cefuroxime may reach the CSF of these patients by diffusion or via active transport. Further studies are warranted regarding the transport mechanisms of cefuroxime via the BBB.

Table II. Systemic infections and treatment

Patient	Onset on day	Systemic infections	Microbiology	Treatment
1	8	pneumonia	*Pseudomonas aeruginosa* *Serratia marcescens*	netilmicin ciprofloxacin
2	9	pneumonia	*P. aeruginosa* *Candida albicans*	amoxicillin + clavulanic acid netilmicin ceftazidime piperacillin
3	14	pneumonia	*P. aeruginosa*	co-trimoxazole ciprofloxacin
4	7	tracheo-bronchial colonisation	*C. albicans* *Streptococcus constellatus* *Klebsiella* spp. *Enterobacter cloacae* *Stenotrophomonas maltophilia*	amoxicillin + clavulanic acid ceftazidime vancomycin
	13	vaginal-mycosis		econazol

In summary, our data show that cefuroxime reaches the CSF, suggesting that this may be a suitable prophylactic antibiotic for the prevention of VRI in patients with TBI. However, aseptic implantation of intraventricular catheters as well as sterile management of the device are essential. A follow-up study will focus on elucidating the exact pharmacokinetics of cefuroxime in the CSF of patients with TBI.

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